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General introduction and outline of the thesis
In the last two decades, treatment of rectal cancer has considerably improved in Europe. Although this applies to most solid malignancies, improvements in the diagnosis and treatment of rectal cancer surpass virtually all others. In the early 1990s, outcome after rectal cancer treatment was poor, with survival and recurrence rates of approximately 45%. Nowadays, survival after rectal cancer is sometimes even better than after colon cancer. While radiotherapy and chemoradiotherapy play an important role in the current, multidisciplinary treatment of rectal cancer, surgery remains the inevitable cornerstone for cure. For each and every improvement in surgical techniques, (neo)adjuvant treatment schedules, imaging and pathology, clinical trials and population-based audit registrations have played a crucial role.

The aim of this thesis is to contribute to further improvements in rectal cancer treatment by investigating the multidisciplinary treatment forms, quality control and European collaboration.

The role of radiotherapy
In the early seventies, local recurrence after rectal cancer surgery was 38% while the majority of those patients never developed distant metastases. Although it was known that radiotherapy could reduce local recurrence, the important question remained whether radiotherapy should be given before or after the operation. Between 1980 and 1985, the 'Uppsala trial' randomised 471 rectal cancer patients to preoperative or postoperative radiotherapy. Post-operative radiotherapy had an inferior tolerance compared with pre-operative radiotherapy. Besides, compliance was dramatic in the postoperative radiotherapy group: 46% of the patients could not start radiotherapy within 6 weeks after the operation because of complicated postoperative recovery. After a mean follow-up of 6 years, local recurrence in the preoperative radiotherapy group was 12% compared with 21% in the postoperative radiotherapy group although there was no difference in survival between the treatment arms.

Simultaneously with the 'Uppsala trial', the 'Stockholm Rectal Cancer Study Group' started the 'Stockholm I' trial, which randomised 849 rectal cancer patients between preoperative 25Gy radiotherapy versus surgery alone. After a median follow-up of 9 years, local recurrence in the irradiated group was 14% against 28% in the surgery alone group. Cancer specific death rate was lower in the irradiated group. However, postoperative mortality within 30 days of surgery was increased after radiotherapy, mainly in elderly patients, which resulted in an equal overall survival in the two arms.

A new study, with the objective to reduce postoperative mortality while the reduction of local recurrences was maintained, applied a reduced radiation volume and excluded patients above 80 years: the Stockholm II trial. Between 1987 and
1993, 557 patients were randomised between either 25Gy radiotherapy followed by surgery within a week, or surgery alone. After a median follow-up of 9 years, local recurrence in the irradiated group was 12% versus 25% in the surgery alone group. With the reduced irradiation volume and the exclusion of aged patients, there was no significant difference in postoperative mortality. Nevertheless, there was still no difference in overall survival.6

Between 1987 and 1990, the ‘Swedish Rectal Cancer Trial’ randomised 1168 patients younger than 80 years with resectable rectal cancer to undergo preoperative 25Gy radiotherapy followed by surgery within one week or to have surgery alone. After five years, the local recurrence ratio in the irradiated group was 11% compared with 27% in the surgery alone group. In contrast to the earlier trials, preoperative radiotherapy improved survival in the Swedish Rectal Cancer Trial: the overall five-year survival rate was 58% in the irradiated group and 48% in the surgery only group.7

The era of total mesorectal excision

In 1979, Heald proposed that mesorectal tissue should be removed together with the tumour to reduce local recurrence.8 Together with Enker he popularised the Total Mesorectal Excision (TME) technique: a complete and sharp excision of the mesorectum under direct vision, with preservation of the hypogastric plexus.9 In the nineties, both TME pioneers convinced the surgical world by showing 5-year local recurrence rates below 10% in rectal cancer patients operated with the TME technique without (neo)adjuvant therapy.10,11

Because all studies showing positive effects of radiotherapy were performed with the conventional surgical technique, while TME surgery alone resulted in low local recurrence rates, the Dutch Colorectal Cancer Group conducted a new clinical trial to study the effects of preoperative radiotherapy in combination with TME surgery: the TME trial.12 The new surgical technique was implemented in a systematic fashion. All participating surgeons were trained in the TME technique by workshops and videotapes. At least five procedures of each participating surgeon were supervised by an instructor surgeon. Pathologists were trained to examine the specimens according to the protocol of Quirke et al. regarding the circumferential resection margin (CRM), lymph nodes and dissection plane.9 Between 1996 and 1999, 1861 patients were randomised for the TME trial. Five-year local recurrence rate were 5.6% with and 10.9% without preoperative radiotherapy and a five-year overall survival of 64% in both groups.14 The twelve year follow-up data of the TME trial are the subject of chapter 2.

In some countries chemoradiotherapy was preferred as a standard therapy for rectal cancer instead of only radiotherapy. The German Rectal Cancer Study Group compared pre-operative chemoradiotherapy with postoperative chemoradiotherapy
for patients with locally advanced rectal cancer patients, operated with TME surgery. Between 1995 and 2002, 421 patients were included. Five-year local recurrence was 6% in the group assigned to preoperative chemoradiotherapy versus 13% in the postoperative chemoradiotherapy group. There was also reduced toxicity in the preoperative chemotherapy group but no survival advantage.\textsuperscript{15}

The Polish Rectal Cancer Trial investigated whether preoperative chemoradiation offered an advantage in sphincter preservation compared with preoperative short term radiation for patients with resectable T3-T4 rectal cancer operated by means of the TME technique. Between 1999 and 2002, 316 patients were included. Despite significant downsizing of the tumor in the chemoradiation group, there was no difference in sphincter preservation, local control, late toxicity or survival.\textsuperscript{16,17}

Because irradiating all rectal cancer patients possibly overtreats certain patient groups, the MRC CR07/NCIC-CTG C016 trial compared 25Gy preoperative radiotherapy with selective postoperative chemoradiotherapy only in patients with an involved circumferential margin. After three years, local recurrence was 4.4% in the group treated with preoperative radiotherapy compared with 10.6% in the selective postoperative chemoradiotherapy group. There was no difference in overall survival.\textsuperscript{18}

\textbf{Adjuvant Chemotherapy for rectal cancer}

In contrast to colonic cancer, there is not much evidence that adjuvant chemotherapy improves survival for rectal cancer patients. The only study that showed an improved survival after chemotherapy is the Japanese 'National Surgical Adjuvant Study of Colorectal Cancer'. Two hundred seventy-six patients with a completely resected stage III rectal cancer were randomised between one year of uracil-tegafur or no adjuvant treatment. Three-year overall survival was 91% in the uracil group against 81% in the surgery-alone group (p=0.005).\textsuperscript{19} However, there are many differences between the treatment regimens given in this trial and the practice in Europe. Selective lateral pelvic lymphadenectomy is routinely performed in Japan, whereas radiotherapy is standard in Europe but not in Japan. Furthermore, uracil is not the regimen of first choice any more.

The EORTC 22921 trial evaluated preoperative and/or postoperative chemotherapy with fluorouracil as addition to preoperative radiotherapy in the treatment of T3/T4 rectal cancer patients. 1011 patients were enrolled in the trial. After a median follow-up of 5 years, chemotherapy showed significant benefits on local recurrence rates. However, it had no effect on survival, regardless whether it was given preoperatively, postoperatively or both.\textsuperscript{20} While patients were enrolled between 1993 and 2003, TME surgery was not introduced until the beginning of 1999.
To evaluate the effect of postoperative chemotherapy for stage II and III rectal cancer patients who are treated with standardised TME surgery, the Dutch Colorectal Cancer Group initiated the PROCTOR (Pre-operative Radiotherapy and/or adjuvant Chemotherapy combined with TME surgery in Operable Rectal cancer) trial in 2000. In 2004, the trial was succeeded by the SCRIPT (Simply Capecitabine in Rectal Cancer after Irradiation Plus TME) Trial. The results of these two trials are the subject of chapter 3.

Despite the sparse evidence for adjuvant chemotherapy for patients treated with preoperative radiotherapy and TME surgery, many oncologists believe adjuvant chemotherapy might still be beneficial for selected rectal cancer patients. Chapter 4 contains an attempt to devise nomograms from a pooled database of the Swedish Rectal Cancer trial, the Dutch TME trial and the Polish Rectal Cancer trial; these might assist in the decision when to treat a rectal cancer patient with adjuvant chemotherapy and how frequent follow-up should be, on the basis of risk stratification for local recurrence and death.

Transanal endoscopic microsurgery
While TME surgery is associated with excellent results on oncological outcome, it can have serious side effects such as faecal and urinary incontinence, sexual dysfunction or a permanent colostomy. Transanal endoscopic microsurgery (TEM) is a minimally invasive surgical technique for the local treatment of rectal adenomas and superficially located malignant lesions that has benefits over total TME surgery in terms of these side effects as well as of hospital stay and costs. The incidence of discovering carcinoma in presumed adenomas can be as high as 34%. Furthermore, a carcinoma presumed to be superficial can show growth in or through muscular layers of the rectum on histological examination. Under certain conditions, a microscopically complete TEM resection can be considered sufficient for T1 rectal cancers combined with follow-up in a ‘wait and see’ regimen. In other patients, the finding of an invasive carcinoma may warrant an additional ‘completion’ TME.

However, little is known about the effect on outcome in terms of tumour recurrence and surgical complications after such ‘completion TME’ following prior TEM in comparison with a primary TME procedure. Chapter 5 is devoted to the consequences of prior TEM followed by completion TME, according to ostomy rate, local recurrence and survival, by comparing these patients with rectal cancer with those from the TME trial treated with what is currently regarded as the optimal treatment regimen in The Netherlands: TME preceded by 5x5 Gy radiotherapy.

Quality Assurance and surgical audit registrations in Europe
The transition from conventional surgery to the quality-controlled multidisciplinary treatment regimen of the TME trial was not limited to the trial population. In
the Netherlands, survival improved for all rectal cancer patients treated in the Comprehensive Cancer Centres South and West. Before the TME trial (1990-1995), five-year overall survival after rectal cancer was 56%, during the trial (1996-1999) it was 62%, and after the TME trial (2000-2002) 65%. What this might mean for the traditional survival backlog of rectal cancer compared with colon cancer is addressed in chapter 6.

In Europe, 5-year relative survival for colorectal cancer still ranges between 32% and 64%. In most western health care systems, efforts are made to reduce hospital variation by focussing on selective referral and encouraging patients to seek care in high-volume hospitals. Such a strategy of treating a larger proportion of patients in specialised centres can evidently improve outcomes for complex surgical procedures, such as esophagectomies and pancreatectomies.

Though everybody involved strives for the best possible care, there is an ongoing and sometimes fierce debate between doctors, politicians and patients about centralizing surgical care to high volume centres. This has led to a growing consensus to concentrate surgical procedures with high risk and a relatively low incidence in high-volume hospitals. On the other hand, the expertise for diagnosis and treatment of common types of cancer should preferably be widespread and easily accessible for all patients. After lung cancer and breast cancer, colorectal cancer is the third most common malignancy worldwide, with 1.15 million new cases every year. Referral of all colorectal cancer patients to a limited number of high volume centres will inevitably decrease convenience for patients and their family. This applies not only to the operation, but also to (neo)adjuvant radiotherapy and many years of follow-up visits. The need for centralisation of colorectal cancer surgery is in the subject of chapter 7, in which a meta-analysis will be performed in order to combine the best available evidence about the volume-outcome relationship for colorectal cancer.

Apart from averages, there will always be low volume providers who perform very well as well as there are high volume providers with unacceptable outcomes. As an alternative to volume-based referral, hospitals and surgeons can improve their results by learning from their local and personal outcome statistics and those from colleagues treating a similar patient group. Surgical audit is a quality instrument that collects detailed clinical data from different health care providers, which can be adjusted for baseline risk and subsequently fed back to individual hospitals or surgeons. In this way, 'best practices' can be identified, communicated and broadly adopted. After case mix adjustments, a fair judgement can be made about the quality of cancer treatments. Not only can hospitals and surgeons be faced with their own results in comparison with those of colleagues treating the same patient category, another important advantage is that audit registries include the entire patient population, which makes it possible to perform research on patient groups that are usually excluded from clinical trials (e.g. the aged and patients...
with severe comorbidity). Since the early 1990’s several European national audit registries in surgical oncology have been set up and have led to improvements with a great impact on outcome.\textsuperscript{26,27} Although all national audits have contributed to improved results, differences remain between European countries that cannot be easily explained. These differences affect mortality, complications, recurrence and survival. Moreover, there are substantial differences in (neo)adjuvant treatment regimens. While in Sweden and the Netherlands most rectal cancer patients receive preoperative radiotherapy, in Norway it is a small minority (4% between 1993 and 1997).\textsuperscript{28} Nevertheless, local recurrence rates in Norway equal the rates in Sweden and the Netherlands.\textsuperscript{16} To generate the best care for colorectal cancer in the whole of Europe and to meet political and public demands for transparency, a better and broader insight in treatment outcomes is needed. A European audit registration can realise transparency, benchmarking and feedback across national borders and can rapidly lead to a decrease in variation and to improved outcomes throughout the continent. Urged by these arguments, the European CanCer Organisation (ECCO) and the European Society of Surgical Oncology (ESSO) initiated an international, multidisciplinary, outcome-based quality improvement program: European Registration of Cancer Care: EURECCA. The goal of EURECCA is to create a multidisciplinary European registration structure for patient, tumour and treatment characteristics; once linked to outcome registration this program can be used for benchmarking and internal feedback among participants and can enhance further improvements in quality and efficiency of cancer care. Which national audit registries in Europe have so far given their full commitment to participate in the EURECCA framework is described in detail in chapter 8.

Once a multidisciplinary European registration structure in which characteristics of patient, tumour, and treatment are linked to outcome may address many important topics that are unanswered by randomised controlled trials. The EURECCA project encompasses existing national audit registrations and has started with colorectal cancer, but in the future other solid tumour types, such as breast cancer, gastric cancer, and oesophageal cancer, will follow. Unfortunately, clinical auditing comes with a price. Despite rapid developments in medical information technology, clinical auditing still is a considerable administrative burden for medical professionals. A beautifully designed but very detailed registry that turns out to be too time-consuming to complete is worthless. Therefore, it is important only to register those items that really matter. When a new audit is set up, dedicated professionals might be tempted to develop a very complete, although unnecessary large dataset. Instead of devising a new registry from scratch, a ‘core dataset’ distilled from existing registries can save much energy. The EURECCA consortium is currently formed by nine independently developed national audit registrations for colorectal tumours, most of which have already run for many years. The cumulative experience of EURECCA’s participants can be used to identify a ‘core dataset’ that covers all important aspects needed for high quality auditing and that at the same time lacks
superfluous items that only consume administrative effort. Even more important than its being used as a template for other audits, an EURECCA core data set will give the consortium insight in what type of research can be performed in the near future. In chapter 9, the data items used by the registries so far participating in EURECCA are compared in order to identify a core dataset and explore options for future research within the EURECCA project.

The variation within Europe in the outcome of treatment for colorectal cancer might be explained by case mix variation, differences in socioeconomic status and by differences in registration. More importantly, many countries have their own national guidelines, with different treatment regimens. These different treatment strategies may well lead to differences in survival.29-31 Currently it is unknown whether the treatment strategy of any country is better than that of the other countries. Most of previous studies about differences in survival between European countries lacked information about stage of disease and about treatment strategies; therefore these results should be interpreted with caution. In preparation to uniform EURECCA guidelines, in chapter 10, a study is reported that sets out to compare preoperative treatment of rectal cancer patients including the differences in tumour stage between some of the European countries participating in the EURECCA-project.

Finally, chapter 11 contains a summary of the results of the separate studies as well as a discussion on the future prospects of multidisciplinary treatment of colorectal cancer and of international quality assurance.

References


